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## **Bivariate relationship between opioid use disorder and suicide attempts despite mental health**

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Does opioid use disorder (OUD) have a potentially causal role in the risk for suicide attempts (SA), or vice versa? The patterns of correlation and causation between them are still not clear due to psychiatric confounding. We aim to investigate their pairwise associations and interrogate the potential bidirectional relationship using genetically based methods. We collected data from UK Biobank, Million Veteran Program, Psychiatric Genomic Consortium, and International Suicide Genetics Consortium. Statistical genetics tools were used to perform epidemiological association, genetic correlation, polygenic risk score (PRS) prediction, and Mendelian randomizations (MR). Analyses were conducted to examine the OUD-SA relationship with and without controlling for psychiatric disease status. Strong correlations between OUD and SA were observed at both phenotypic level (overall samples [OR=2.94, P =1.59x10<sup>-14</sup>]; non-psychiatric subgroup [OR=2.15, P =1.07x10<sup>-3</sup>]) and genetic level (r<sup>2</sup>=0.4 and 0.5 with or without conditioning on major depression disorder). The higher genetic susceptibility to SA can increase the polygenic risk of OUD (OR=1.08, false discovery rate [FDR] =1.71x10<sup>-3</sup>), while the higher susceptibility to OUD can also increase the risk of SA (OR=1.09, FDR =1.73x10<sup>-6</sup>). A combination of different MR analyses suggested a possible causal association from SA to OUD (2-sample univariable MR: OR=1.14, P = 0.001; multivariable MR: OR=1.08, P = 0.001). This genomics-based study supports a strong genetic association underlying the OUD-SA comorbidity. Though both phenotypes are intertwined with other psychiatric disorders, there also exists an independent bidirectional relationship between OUD and SA.